I. AMENDMENT

Please make the following amendments.

In the Specification:

On page 15 please replace the phrase "FIG. 17" with "FIG. 17A-17C".

On page 15 please replace the phrase "FIG. 18" with "FIG. 18A-18B".

In the Claims:

Please cancel claim 17, 24 and 32, without prejudice or disclaimer.

Please amend claims to read as follows.

1. (Twice amended) A method for inhibiting the growth of a cancer cell comprising

(i) contacting the cancer cell with a thiazolidinedione compound; and

(ii) contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with X-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell;

wherein, the chemotherapeutic drug is an alkylating agent, an antimetabolite, an antitumor antibiotic, a corticosteroid hormone, a mitotic inhibitor, a nitrosurea, or a tumor necrosis factor.

18. (Amended) The method of claim 16, wherein the chemotherapeutic drug comprises an alkylating agent.

19. (Amended) The method of claim 16, wherein the chemotherapeutic drug comprises a mitotic inhibitor.

20. (Amended) The method of claim 16, wherein the chemotherapeutic drug comprises an antibiotic.

21. (Amended) The method of claim 16, wherein the chemotherapeutic drug comprises a nitrosourea.

22. (Amended) The method of claim 16, wherein the chemotherapeutic drug comprises an antimetabolite.

23. (Amended) The method of claim 16, wherein the chemotherapeutic drug comprises a corticosteroid hormone.

26. (Amended) The method of claim 16, wherein the thiazolidinedione and the chemotherapeutic drug are suitably dispersed in a pharmacologically acceptable formulation.

33. (Twice amended) A method for treating cancer in a patient comprising administering to the patient troglitazone and a chemotherapeutic drug in an amount effective to produce a therapeutic benefit; wherein, the chemotherapeutic drug is an alkylating agent, an antimetabolite, an antitumor antibiotic, a corticosteroid hormone, a mitotic inhibitor, a nitrosurea, or a tumor necrosis factor.

35. (Amended) A method of treating cancer in a patient comprising administering to the patient a therapeutically effective amount of troglitazone and a chemotherapeutic drug; wherein, the chemotherapeutic drug is an alkylating agent, an antimetabolite, an antitumor antibiotic, a corticosteroid hormone, a mitotic inhibitor, a nitrosurea, or a tumor necrosis factor.

36. (Twice amended) A method for treating microscopic residual cancer comprising the steps of:

(i) identifying a patient having a resectable tumor;

(ii) resecting said tumor; and

(iii) contacting the tumor bed with a therapeutically effective amount of troglitazone and a chemotherapeutic drug;

wherein, the chemotherapeutic drug is an alkylating agent, an antimetabolite, an antitumor antibiotic, a corticosteroid hormone, a mitotic inhibitor, a nitrosurea, or a tumor necrosis factor.

37. (Twice amended) A method for treating a subject having a tumor comprising the steps of:

(i) surgically revealing said tumor; and

(ii) contacting said tumor with a therapeutically effective amount of troglitazone and a chemotherapeutic drug;

wherein, the chemotherapeutic drug is an alkylating agent, an antimetabolite, an antitumor antibiotic, a corticosteroid hormone, a mitotic inhibitor, a nitrosurea, or a tumor necrosis factor.

38. (Twice amended) A method for treating a subject having a tumor comprising the step of perfusing said tumor, over an extended period of time, with a therapeutically effective amount of troglitazone and a chemotherapeutic drug; wherein, the chemotherapeutic drug is an alkylating agent, an antimetabolite, an antitumor antibiotic, a corticosteroid hormone, a mitotic inhibitor, a nitrosurea, or a tumor necrosis factor.

41. (Amended) A method for inhibiting the growth of a cancer cell comprising:

(i) contacting the cancer cell with a composition comprising troglitazone; and

(ii) contacting the cancer cell with a chemotherapeutic agent or irradiating the cancer cell, in amounts effective to inhibit growth of the cancer cell;

wherein, the chemotherapeutic drug is an alkylating agent, an antimetabolite, an antitumor antibiotic, a corticosteroid hormone, a mitotic inhibitor, a nitrosurea, or a tumor necrosis factor.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims and Specification

Claims 1-46 were rejected by the Office Action dated July 01, 2002. Claim 32 stands rejected under 35 U.S.C. § 112, first paragraph. Claims 1-8, 16-23, 28, 30, 33-35 and 40-41 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Urban (U.S. Patent No. 5,814,647) as evidenced by Medenica *et al.* (U.S. Patent No. 5,736,129), Knight *et al.* (U.S. Patent No. 6,090,407) and Roth *et al.* (U.S. Patent No. 5,747,469). Claims 1-31 and 33-46 stand rejected under 35 U.S.C. § 103(a) as being obvious over Tontonoz *et al.* (Proc. Natl. Acad. Sci. 94:237-241) in view of Urban (U.S. Patent No. 5,814,647), Medenica *et al.* (U.S. Patent No.

5,736,129), Knight *et al.* (U.S. Patent No. 6,090,407), and Roth *et al.* (U.S. Patent No. 5,747,469). The specific grounds for rejection, and the Applicants' response thereto, are set out in detail below.

Claims 1, 18-23, 26, 33, 35-38, and 41 have been amended. Claims 17, 24, and 32 have been canceled; Applicants reserve the right to pursue these claims in any continuing application. Support for amendments to claims 1, 33, 35-38 and 41 can be found in the specification at least on page 20, line 6 to page 39, line 19. Support for the amendment to claim 18 can be found at least on page 20 line 20. Amendments to claims 18-23 either correct misspellings or modify the dependency of a claim due to the cancellation of claim 17. A copy of the claim amendments can be found in Appendix A. Thus, claims 1-16, 18-23, 25-31 and 33-46 are currently pending. A copy of the pending claims is included as Appendix B for the examiner's convenience.

B. Objection of claim 18

The Action objects to claim 18 due the misspelling of "alkylating." Appropriate correction has been made by amendment herein. Withdrawal of the objection is requested.

C. Objection to specification

The Action objects to the specification based on the phrases "FIG. 17" and "FIG. 18", when in fact there are FIG. 17A-17C and FIG. 18A-18B. Appropriate correction has been made by amendment herein. Withdrawal of the objection is requested.

D. Rejection of Claim 32 under 35 U.S.C. § 112, first paragraph

The Action rejects claim 32 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Action states that the claim encompasses gene therapy for the treatment of

cancer *in vivo*, and due to the unpredictability in the art, it would require undue experimentation to practice the invention. Applicants respectfully traverse this rejection.

The Action applies broad general statements that are directed mainly to the therapy of inherited genetic disorders or to therapies held to standards above and beyond those of patentability. Applicants note that the Action references an issued gene therapy patent of Roth *et al.* as supporting rejections under 35 U.S.C. §102(e) and 103. In the interest of expediting prosecution and presenting claims in better form for appeal, Applicants have canceled claim 32.

E. The Claims Are Not Anticipated by the Cited References

The Action rejects claims 1-8, 16-23, 28, 33-35 and 40-41 under 35 U.S.C. §102(e) as being anticipated by Urban *et al.* (U.S. Patent No. 5,814,647) ("Urban") as evidenced by Medenica *et al.* (U.S. Patent No. 5,736,129) ("Medenica"), Knight *et al.* (U.S. Patent No. 6,090,407) ("Knight") and Roth *et al.* (U.S. Patent No. 5,747,469) ("Roth"). The Action states that Urban teaches that troglitazone and related thiazolidinedione compounds can be used in the treatment of climacteric and cancer. It also states that Urban suggests the use of troglitazone therapy in conjunction with chemotherapeutic agents, radiation, or surgery. However, Urban does not specifically teach the chemotherapeutic drugs or types of radiation to be used. The Action argues that the types of chemotherapeutic drugs and the types of radiation used in the treatment of cancer are well known in the art as evidenced by Medenica, Knight, and Roth. Applicants respectfully traverse this rejection.

The Applicants' invention is directed towards a method for inhibiting the growth of a cancer cell by treating the cancer with a combination of a thiazolidinedione compound with other therapies, some of which are standard therapies. In particular, the methods of the presently claimed invention comprise contacting the cancer cell with a thiazolidinedione compound and

contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with x-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell. Prior to the Applicants' disclosure the use of thiazolidinedione therapy in combination with other chemotherapeutic agents or radiation for treatment of a cancer cell was not taught in the art.

Furthermore, for a prior art disclosure to anticipate an applicant's invention, the reference must contain an "enabling disclosure." MPEP §2121.01 (quoting *In re Hoeksema*, 399 F.2d 269, 158 U.S.P.Q. 596 (C.C.P.A. 1968)). The Urban reference does not contain an enabling disclosure. As stated in the Action on page 11: "...Urban does not teach specifically the types of chemotherapeutic drugs and the types of radiation used in combination with the troglitazone therapy..."

In addition, the Action dated July 01, 2002 admits that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." The Action at page 6 citing Genentech, Inc. v. Novo Nordisk A/S, 42 USPQ 2d 1001. Urban fails to enable the use of troglitazone in combination with chemotherapeutic drugs or radiation. Urban merely states, "Use of Troglitazone therapy in conjunction with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient." Not a single working example is provided. At most, combination therapy, as described in Urban, was a mere germ of an idea that is not supported by disclosure.

The Action continues by arguing that this deficiency may be remedied by citing references teaching the use of chemotherapeutic agents or radiation treatments either as a monotherapy or a multiple drug therapy. None of the secondary references teach or suggest a combination with thiazolidinedione therapy. Applicants note, for example, that the teaching in Urban, alone or in combination with Medenica, Knight, and Roth, does not provide any teaching that would have lead one skilled in the art to predict that the combination therapy taught in the instant specification would have resulted in a reduction of 5-FU dose by a factor of 100 (see at least page 57 lines 25-28 and FIG. 5).

Moreover, the references of Medenica, Knight, and Roth do not remedy the defect in Urban. They are not proper references. The use of multiple references for anticipation is not applied correctly. Multiple references may be used for a) to prove that the primary reference contains an enabling disclosure, b) to explain the meaning of a term used in the primary reference, or c) to show that a characteristic not disclosed in the reference is inherent (MPEP 2131.01). The Action purports to cite the reference to reason (a). However, the Medenica, Knight, and Roth references fail to provide enablement for treating cancer by using a combination of *thiazolidinedione* with other chemotherapeutic agents or radiation. In fact none of the references describe or mention the use of thiazolidinedione in combination with other chemotherapeutic agents or radiation. At most the secondary references provide enablement for single drug therapies and some multiple drug therapies that do **not** include thiazolidinedione compounds in combination with other chemotherapeutic agents or radiation.

Accordingly, for the above reasons, Applicants contend that the claims are not anticipated and respectfully request that the rejection be withdrawn.

F. The Claims Are Non-obvious over the Cited References

The Action rejects claims 1-31 and 33-46 under 35 U.S.C. § 103(a) as being obvious over Tontonoz *et al.* (*Proc. Natl. Acad. Sci.* 94:237-241) ("Tontonoz") in view of Urban (U.S. Patent No. 5,814,647), Medenica *et al.* (U.S. Patent No. 5,736,129), Knight *et al.* (U.S. Patent No. 6,090,407), and Roth *et al.* (U.S. Patent No. 5,747,469). The Action alleges that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method disclosed by Tontonoz by combining the use of a thiazolidinedione compound in conjunction with other chemotherapeutic agents to inhibit the growth of liposarcoma cells or mesenchymal tumor cells or tumor cells expressing PPARγ as taught by Urban. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the teaching of the claimed combination and the reasonable expectation of success must both be found in the prior art. MPEP §2143 (citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). Furthermore, the cited references must teach or suggest that the references be combined. A proper prima facie case has not been made because these requirements have not been fulfilled.

Tontonoz, in fact, teaches *away* from combining thiazolidinedione therapy with chemotherapeutic drugs or radiation by recommending the use of thiazolidinedione compounds as an alternative to conventional chemotherapy (Tontonoz, p. 241, second full paragraph). Furthermore, the presently cited references do not teach or suggest that the references be combined. Also, Tontonoz describes a combination of two compounds that act on the same molecular entity, a PPARγ/RXRα heterodimer. The teaching of Tontonoz is essentially a method of fully activating a receptor controlling differentiation. Tototonoz does not contain any suggestion or motivation to combine its teachings with other references beyond PPARγ/RXRα

ligands. Urban is said to disclose the use of troglitazone therapy in conjunction with other chemotherapeutic agents or radiation; however, Urban does not teach the use of any specific chemotherapeutic drugs or types of radiation and is not enabling for a treatment combining thiazolidinedione therapy with chemotherapeutic drugs or radiation, as described above.

The Urban reference is not enabled for a "method for inhibiting the growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound and contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with x-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell." Furthermore, none of the other references remedies this defect. Therefore, there is no reasonable expectation of success at practicing the claimed invention. Accordingly, there is no *prima facie* case of obviousness.

At most, the references disclose that one skilled in the art might find it "obvious-to-try" the claimed invention. An "obvious-to-try" situation exists when a general disclosure piques the scientist's curiosity, "such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990). The Federal Circuit has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725, 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990).

Accordingly, for the above reasons, Applicants contend that the claims are not obvious and respectfully request that the rejection be withdrawn. Applicants note that the pending claims